Common Drug Review
Patient Group Input Submissions

mepolizumab (Nucala) for asthma, severe eosinophilic

Patient group input submissions were received from the following patient groups. Those with permission to post are included in this document.
Asthma Society of Canada/National Asthma Patient Alliance — permission granted to post.
Ontario Lung Association — permission granted to post.

CADTH received patient group input for this review on or before January 18, 2016.

CADTH posts all patient input submissions to the Common Drug Review received on or after February 1, 2014 for which permission has been given by the submitter. This includes patient input received from individual patients and caregivers as part of that pilot project.

The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations. While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

Asthma Society of Canada/National Asthma Patient Alliance

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		NucalaTM (mepolizumab) for add-on maintenance treatment of adult patients with severe eosinophilic asthma
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1.1 Submitting Organization

The Asthma Society of Canada (ASC) is a registered charitable organization whose mission is to be the balanced voice for asthma in Canada, advancing optimal self-management, prevention, research, and health care. Its vision is to empower every child and adult in Canada with asthma to live an active and symptom-free life. The ASC is based in Toronto under the direction of a volunteer Board of Directors, and provides its services directly to people with asthma through Web sites, e-mail, and the Asthma & Allergy HelpLine. Individuals with asthma are invited to join the National Asthma Patient Alliance (NAPA), the ASC's grassroots patient group providing asthma support, education, and advocacy. NAPA has an outreach to over 5,000 asthma and allergy patients, caregivers, and other interested participants, from all regions of Canada.

1.2 Conflict of Interest Declarations

a) We have the following declaration(s) of conflict of interest in respect of corporate members and joint working, sponsorship, or funding arrangements:

The patient research that forms a significant part of this submission was supported by educational grants from Novartis Pharmaceuticals Canada Inc., Roche Canada, Boston Scientific Ltd., GlaxoSmithKline, AstraZeneca, Boehringer-Ingelheim International, Merck, Takeda, Teva Innovation Canada, Sanofi, Sanofi Pasteur, Pfizer, and Johnson & Johnson. We do not have any conflicts of interest with regard to corporate members and joint working arrangements.

b) We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission:

The ASC requested and received a medical briefing from GlaxoSmithKline previously with regard to Nucala. We did not receive any additional assistance in compiling this submission.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

The majority of the patient impact information in this section is drawn from a study conducted by the Asthma Society of Canada in 2014, entitled "Severe Asthma: The Canadian Patient Journey". A copy of the full study report can be viewed here. This study included Canadian adults 18 years or older who live with Severe Asthma as defined by their symptoms, their level of asthma control, and a review of their clinical profiles by a team of expert advisors. Twenty-four patients participated in in-depth personal interviews about their condition and its impact on their personal, social, medical, and economic circumstances. A complementary on-line quantitative survey of 200 individuals with Severe Asthma was conducted to validate and quantitate the in-person findings. Further details of the study population, investigators, and process are available on pages 28 to 31 of the full report.

Additional details of disease definitions and treatment options have been drawn from material published on the ASC's Web site, the Canadian Product Monograph and US Prescribing Information for Nucala (mepolizumab), and a PubMed search for relevant treatment guidelines and review articles.

2.2 Impact of Condition on Patients

Definitions and statistics

Asthma is a chronic disease characterized by inflammation in the airways. Symptoms of asthma include wheezing, coughing, shortness of breath, and a sensation of tightness in the chest. Asthma symptoms can occur in both a low-grade chronic manner and also as more sudden, severe attacks known as exacerbations, which can be triggered by a variety of allergic and non-allergic causes. Information from Statistics Canada and the Public Health Agency of Canada shows that approximately 3 million Canadians live with some degree of asthma, with approximately 150,000 to 250,000 of these cases being classified as Severe Asthma. (Life and Breath: Respiratory Disease in Canada)

Although no universally accepted dividing line has been established between "severe" and nonsevere asthma, the recent international guidelines of the European Respiratory Society and the American Thoracic Society (Chung 2014) recommend classifying patients' asthma as severe if it is still uncontrolled in spite of optimal use of long-term controller and short-acting reliever medications (see section 2.3 for more detail on medication types). According to the guidelines of the Global Initiative for Asthma (GINA), asthma can be considered "uncontrolled" if during the past 4 weeks the patient has experienced **at least 3** of the following: (GINA Global Strategy for Asthma Management and Prevention):

- Daytime asthma symptoms more than twice a week
- Any night waking due to asthma
- Reliever medication needed more than twice a week (not including reliever taken before exercising)
- Any activity limitation due to asthma

Eosinophilic asthma is a subtype of asthma that is characterized by the presence of eosinophils in the inflamed tissues, which can be detected through examination of sputum. In contrast to more classic forms of asthma that tend to be linked to a particular allergic trigger and diagnosed earlier in life, many

cases of eosinophilic asthma only appear in adulthood, in patients with few or no allergies. The initial approach to treatment is similar as in patients with allergic asthma – inhaled controller and reliever medications – but often also extends to oral corticosteroids if initial inhaled corticosteroid treatment is inadequate. Even with the use of inhaled and/or oral steroids, many cases of eosinophilic asthma remain uncontrolled and therefore classified as "severe". (de Groot 2015)

Impact of severe (uncontrolled) asthma on patients

Severe Asthma has many different effects and consequences that can impair patients' quality of life. In the ASC's recent patient journey study, respondents identified several crucial areas where asthma had a major impact: (Severe Asthma: The Canadian Patient Journey)

- **Physical activity**: Over 70% of survey respondents reported limitations to daily activities and exercise due to their asthma, even though 89% agreed that, ideally, asthma should not be a reason for avoiding physical exertion
- **Social interactions**: Almost 2/3 of respondents said that they have felt stigmatized because of their asthma at some point, and that asthma interferes with their social activities and interactions with others
- **Work/school productivity**: More than half of respondents mentioned that asthma has affected their attendance and/or performance at work or school, with about 40% of these saying it affected them "a great deal"
    - About 30% of respondents mentioned that asthma had caused them to miss days of work or school in the previous year; of these, about 2/3 missed 5 days or more, and about 1/3 reported missing more than 10 days
- **Emergency room visits and hospitalization**: About half of respondents had needed to visit an emergency room in the previous year because of asthma symptoms. One-third went more than once during this period, and one in five needed to be hospitalized

Patient quotes:
"I'm just so tired that I can't do anything anymore. Severe Asthma has changed everything."
"I can't even take my son hiking because of my health. My limitations affect other people and it makes me angry that I can't do the things other can and that I used to be able to do."

2.3 Patients' Experiences With Current Therapy

In current Canadian practice, the cornerstones of asthma management are:

- Identification and avoidance of triggers that worsen symptoms and/or cause exacerbations
- Long-term controller medication(s) taken on a regular, ongoing basis to reduce inflammation and reactivity in the airways. The most common controllers are inhaled corticosteroids (ICS) delivered through a "puffer"; these can be used with or without other add-ons such as leukotriene receptor antagonists and long-acting bronchodilators. For patients requiring a higher corticosteroid dose than an inhaler can deliver, oral corticosteroids (OCS) may be used; this is particularly common in patients with severe eosinophilic asthma
- A short-acting reliever (bronchodilator) taken as needed through a puffer to provide rapid relief of exacerbations or severe symptoms

While these measures are adequate to control asthma symptoms and exacerbations in patients with milder disease, by definition a patient whose asthma has been classified as "severe" has tried the standard options and is still experiencing symptoms of a severity and/or frequency that can drastically

reduce quality of life as outlined in section 2.2. The definition of Severe Asthma therefore carries within it an unmet need for treatment options that go beyond the existing standard of care.

In addition to the unmet needs experienced by all patients with Severe Asthma, the distinctive nature of eosinophilic asthma means that some of the novel treatment options for other forms of asthma are not appropriate. One of the newer options for treatment of uncontrolled allergic asthma is omalizumab, an antibody that reduces patients' sensitivity to inhaled allergens by targeting immunoglobulin E. However, since many cases of eosinophilic asthma are non-allergic in nature, omalizumab will be of limited use in this population. Therefore, if a targeted biologic approach is to be used in eosinophilic asthma, it will be necessary to focus on non-allergic targets that are more specific to the eosinophilic pathology, such as the key eosinophil-modulating cytokine IL-5 for mepolizumab.

Patients' use of current therapies

The ASC's recent patient research reveals that many patients do not use their medications appropriately and are not well equipped to manage their Severe Asthma. Many respondents do not carry their short-acting reliever medication with them, and more than half admit to not regularly taking their long-term controller medication. Most often this was due to patients' perception that they were asymptomatic and did not need to continue taking their controller medication. This indicates both a lack of understanding regarding the purpose and goals of controller treatment, as well as perhaps a misperception on the patients' part that their asthma is well controlled. Other reasons cited for not using medications as directed included lack of efficacy (repeated exacerbations despite past use) and unpleasant side effects. (Severe Asthma: The Canadian Patient Journey)

Financial barriers to optimal asthma control

Financial considerations are another important barrier to optimal asthma medication use. In the ASC's survey, about one third of patients reported that they had skipped filling a prescription for an asthma medication because they were unable to afford it. Many private insurers do not provide complete coverage for asthma medications, placing a significant portion of the burden on patients. Since many patients with Severe Asthma have low incomes (more than one-third of survey respondents had household incomes under $50,000) and/or are unable to work because of their asthma, even having to pay a small percentage of the drug cost can be a significant financial concern. (Severe Asthma: The Canadian Patient Journey)

> *Patient quotes:*
> *"I have prescription coverage that will cover birth control, but it won't cover my inhaler. Sometimes I just want to give up."*
> *"My doctors help me with the cost by giving me samples of most of my inhalers, but when I have to pay for them…I have to take on extra work to help pay for my medication."*

Specific concerns with oral corticosteroids

The use of OCS in patients who fail to achieve adequate asthma control with ICS deserves special mention because of the short-term and long-term side effects of systemic corticosteroids. This issue is of particular concern in the population of patients with severe eosinophilic asthma, where many patients depend on long-term OCS to provide some degree of inflammation control after other options prove to be inadequate (de Groot 2015).

Since the activity of ICS is mainly localized to the lungs and airways, the risk of systemic side effects is low and they can be used long-term with few serious safety concerns. On the other hand, OCS can have

significant systemic adverse effects, both in terms of physical changes (e.g., cataracts, bone density changes, suppression of adrenal gland activity) and patients' psychological and emotional well-being (e.g., irritability, agitation, insomnia). Both types of effects can have a significant impact on patient health and quality of life; as such, the recommended practice is to use systemic steroids for as short a duration as possible, and to approach long-term use with caution and regular monitoring. Although this principle and the adverse effects of long-term OCS are well established, the burden of OCS use is not often evaluated in asthma clinical studies and is not well interrogated by the existing asthma-related and general health HRQOL scales, so the real impact of OCS use on patient experience and the improvements associated with OCS discontinuation may be even greater than we know. (Hyland 2015)

Even so, clinical studies in patients with Severe Asthma have demonstrated that patient quality of life, as measured by validated HRQOL scales, improves significantly when a non-OCS add-on medication is introduced that allows patients to stop the OCS. (Nelson 1999, Schmier 2003) While equivalent studies have not yet been performed in the severe eosinophilic asthma population or for mepolizumab specifically, since many of the HRQOL improvements are linked to the elimination of OCS-related side effects, it should be possible to extrapolate these findings to patients who are able to reduce or discontinue OCS after receiving mepolizumab (see section 3.2).

2.4 Impact on Caregivers

Since the focus of this application is a medication that is indicated for adult patients only, it will not go into detail regarding the significant challenges for parent caregivers of children with asthma. In terms of the impact on people who must live with and/or care for an adult with Severe Asthma, the burden of helping with acute exacerbations, trips to the hospital, and other aspects of Severe Asthma has not been specifically quantitated, but based on the comments from patients regarding their interactions with others, the following could be anticipated:

- Inability to do certain physical activities with their family member who has Severe Asthma
- Interruptions to sleep – 80% of survey respondents with Severe Asthma reported that asthma caused sleep disruptions for either themselves or their family members in the past 3 months
- Heightened stress and anxiety due to the constant need to be on alert for asthma exacerbations
- Stress, time, and financial impact (e.g., time off work) associated with accompanying the family member to the emergency room

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

Information on mepolizumab was gathered through a PubMed search of the published literature and a detailed reading of the Canadian Product Monograph and US Prescribing Information for Nucala

3.2 What Are the Expectations for the New Drug or What Experiences Have Patients Had With the New Drug?

a) Based on no experience using the drug:

For patients with severe (uncontrolled) asthma, the major marker of treatment success is for their asthma to be brought under control so that it no longer qualifies as "severe". Depending on the patient's particular clinical profile, this could involve improvements in lung capacity, reductions in the number of exacerbations (particularly those involving hospitalization), and less frequent and/or less severe airway symptoms overall. For patients with severe eosinophilic asthma, many of whom still have

uncontrolled asthma in spite of using standard medications (and potentially OCS), the prospect of a targeted therapy that could address their specific disease in the same way that omalizumab does for allergic asthma is likely to be attractive and encouraging.

In the ASC's survey, patients with Severe Asthma identified their top unmet needs in asthma care generally; these are not specific to mepolizumab or any other novel agent, but give an overall indication of areas that could be addressed to make a major impact on patients' lives. The top 5 goals that respondents would like to achieve are: (Severe Asthma: The Canadian Patient Journey)

- Function normally while completing household activities, walking, and enjoying life
- Not have to visit the emergency department or be admitted to hospital
- Sleep without nighttime symptoms
- Exercise without asthma symptoms
- Go to work

b) Based on patients' experiences with the new drug as part of a clinical trial or through a manufacturer's compassionate supply:

The clinical development program for mepolizumab included two key trials that evaluated endpoints that have a direct impact on the patient experience.

<u>The MENSA trial – reduction in exacerbations and improvement in QoL</u>

The pivotal trial supporting mepolizumab's approval for severe eosinophilic asthma was the MENSA study, a randomized, placebo-controlled trial in 536 patients. Patients were randomized to continue receiving their existing ICS treatment, plus either placebo or add-on mepolizumab (either subcutaneous or intravenous). Compared the ICS-only (placebo) group, subcutaneous mepolizumab showed significant efficacy on the following endpoints that can be directly linked to the patient experience: (Ortega 2014)

- 53% reduction in the frequency of exacerbations. Since the median number of annual exacerbations experienced by respondents in the ASC survey was slightly more than 5, this would correspond to eliminating approximately 3 of those attacks per year.
- 61% reduction in number of exacerbations requiring hospitalization. In the ASC survey, one in five patients reported having been admitted to hospital for asthma-related reasons in the previous year; if similar mepolizumab efficacy is seen in real life, the rate would decline to one patient out of every 13.
- Significantly better quality of life, as measured by the St George's Respiratory Questionnaire (SGRQ), which includes questions on respiratory symptoms and their consequences, including limitations to physical activity, impact on employment, experience of stigmatization, use of medication, side effects of treatment, and effects on psychological well-being. Patients receiving subcutaneous mepolizumab had an overall SGRQ score 7.0 points higher than the placebo group; the number of difference required for the effect to be considered "clinically significant" is 4.0. The analysis did not break down the impact of mepolizumab treatment on the various subscales and facets of patient experience; further trials to pinpoint the impact of mepolizumab on HRQOL are currently underway.

<u>The SIRIUS trial – ability to reduce or stop OCS treatment</u>

A randomized placebo-controlled trial in 135 patients with severe eosinophilic asthma evaluated whether subcutaneous mepolizumab allowed patients receiving OCS to reduce or discontinue their dose, while still maintaining adequate asthma control. On average (median), patients receiving

mepolizumab were able to reduce OCS dose by 50% (versus no reduction in the placebo group), without any loss of asthma control; indeed, the mean number of exacerbations in the mepolizumab group was 32% lower than for placebo, even in spite of the lower OCS usage. 23% of mepolizumab patients (versus 11% in the placebo group) were able to reduce their OCS dose by 90% or more, or to stop taking it altogether. (Bel 2014) Although a formal evaluation of HRQOL was not conducted in this study, the benefits of providing asthma control through non-OCS agents that allow for the withdrawal of OCS have been demonstrated elsewhere (see section 2.3) and should also be applicable in this population.

References

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Ontario Lung Association

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		Name = Mepolizumab Indication = Asthma, severe eosinophili
Name of the patient group		Ontario Lung Association
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1.1 Submitting Organization

The Ontario Lung Association is a registered charity that assists and empowers people living with or caring for others with lung disease. It is a recognized leader, voice and primary resource in the prevention and control of respiratory illness, tobacco cessation and prevention, and air quality and its effects on lung health. The Association provides programs and services to patients and health-care providers, invests in lung research and advocates for improved policies on lung health. It is run by a board of directors and has approximately 70 employees, supported by thousands of dedicated volunteers and works out of a provincial office in Toronto and nine community offices throughout Ontario. The Ontario Lung Association is part of a federated model and works closely with 9 other provincial lung associations and the Canadian Lung Association.

1.2 Conflict of Interest Declarations

a) We have the following declaration(s) of conflict of interest in respect of corporate members and joint working, sponsorship, or funding arrangements:

The Ontario Lung Association receives sponsorship and grants from a number of pharmaceutical companies which support educational and research initiatives. Companies who provide funding to the Ontario Lung Association include: Pfizer, GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Merck, Novartis, J&J, Roche, RX&D, Eli Lilly and the Ontario Home Respiratory Services Association (OHRSA). None of these organizations participated in any way in this submission.

b) We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission:

(Nothing to declare)

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

The information provided in section two was obtained from 5 recently completed on-line surveys by people living with asthma, as well as input from a certified respiratory educator.

2.2 Impact of Condition on Patients

The symptoms and challenges that people experience as a result of Asthma are coughing (with or without mucus), wheezing, shortness of breath, difficulty fighting infections and fatigue. When asked whether this condition affected their day-to-day life, respondents indicated that it did indeed impact both their physical and leisure activities, as well as their financial situation and family relationships. Activity restriction was noted several times throughout the survey. A couple of direct quotes are:

- "It can limit or restrict activities, interfere with work (both in terms of attendance and concentration and performance while at work) and make daily activities more difficult."
- "I would like no restrictions in activities."

The aspects of the condition that are most important to control for people living with it are shortness of breath, coughing, wheezing and fatigue. They would also like to have improved energy levels and a better ability to fight infections.

2.3 Patients' Experiences With Current Therapy

Treatments tried by those who completed the survey included: ICS and LABA (Symbicort), LAAC (Spiriva Respimat), Antihistamine (Reactine 20 mg BID), Antileukotriene (Singulair), SABA (Ventolin) PRN, and one person had just started anti-IGE (Xolair).

Current treatments do provide some relief for: shortness of breath, cough, poor appetite and the decreased ability to fight infection, but patients also indicated they want to experience a greater improvement of these symptoms and their overall goal was less of a medication burden. The only side effects indicated from using the above-mentioned drugs included low energy.

When asked about whether the treatments affected their life in any other way, the respondents indicated that the time required to travel to health-care settings, the time required off work for these appointments and the changes to their daily routine to accommodate treatment did impact their life in a negative way.

Section 3 — Information about the Drug Being Reviewed

3.2 Information Gathering

The information provided in section two was obtained from 5 recently completed on-line surveys by people living with asthma, as well as input from a certified respiratory educator.

3.2 What Are the Expectations for the New Drug or What Experiences Have Patients Had With the New Drug?

a) Based on no experience using the drug:

Key treatment outcomes of asthma that patients would most like addressed are: reduced shortness of breath, reduced coughing, reduced fatigue and improved appetite. They would like an improved ability

to fight infections and to have a higher energy level. Ideally, patients would experience an improved quality of life and improved lung function.

b) Based on patients' experiences with the new drug as part of a clinical trial or through a manufacturer's compassionate supply:

No patients within this evidence group submission has used the drug Mepolizumab.